

**EVIDENCE ON THE CARCINOGENICITY OF
QUINOLINE
AND ITS STRONG ACID SALTS**

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PREFACE

The Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code 25249.5 *et seq.*) requires that the Governor cause to be published a list of those chemicals “known to the state” to cause cancer or reproductive toxicity. The Act specifies that “a chemical is known to the state to cause cancer or reproductive toxicity...if in the opinion of the state’s qualified experts the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity.” The lead agency for implementing Proposition 65 is the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency. The “state’s qualified experts” regarding findings of carcinogenicity are identified as the members of the Carcinogen Identification Committee of the OEHHA Science Advisory Board (22 CCR 12301).

Quinoline was discussed as a high priority candidate for Committee review during a public committee meeting held in Sacramento, California on July 22, 1996 and at a public workshop held November 15, 1996. Public input was solicited on the priority of this chemical in two public comment periods, each of 60 days duration. Once the chemical was selected for Committee review, a public request for pertinent information was made.

This draft document *Evidence on the Carcinogenicity of Quinoline and Its Strong Acid Salts* was developed to provide the Committee with relevant information for use in its deliberations, and reviews the available scientific evidence on the carcinogenic potential of quinoline and its strong acid salts. The meeting where the Committee is to discuss this evidence has been tentatively scheduled for September 25, 1997. Written public comment on the document should be submitted to OEHHA by August 20, 1997, if it is to be considered by the Committee in advance of the meeting. During the September meeting, the public will be given the opportunity to present verbal comment to the Committee.

1 EXECUTIVE SUMMARY

Quinoline is a naturally occurring heterocyclic aromatic chemical found in creosote and other products produced from fossil fuels. It is produced by combustion of a variety of substances including tobacco and is used in the chemical industry. Strong acid salts of quinoline, including the hydrochloride, can be expected to exist in a dissociated state in solution and *in vivo*, and thus are considered toxicologically equivalent to the free or protonated base forms.

Administration of quinoline in feed to male rats produced a significant increase in the incidence of vascular tumors (hemangiomas or hemangiosarcomas) of the liver in three studies. Quinoline in the diet produced a high incidence of hepatocellular tumors and hemangioendotheliomas in male and female mice in one study that lacked untreated controls. It did not produce a significant increase in the incidence of tumors in hamsters or guinea pigs, but the duration of these studies was so short (30 weeks) that they are uninformative. Quinoline did not produce tumors when administered by *s.c.* injection to male and female newborn rats. When administered by *i.p.* injection to newborn mice, it produced liver tumors in males but not in females in three studies. Quinoline initiated skin tumors following dermal application to female mice.

Quinoline produced mutations in bacteria in the presence of metabolic activation, unscheduled DNA synthesis in rat hepatocytes, and DNA adducts *in vitro* in the presence of metabolic activation.

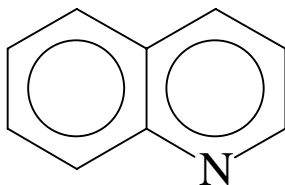
Based on the information reviewed in the preparation of this document, there is evidence for the carcinogenicity of *quinoline and its strong acid salts* at the same site (liver) in two species. Observations of genetic toxicity contribute to the weight of evidence.

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2 INTRODUCTION

2.1 Identity of Quinoline



Quinoline: C₉H₇N

Molecular Weight = 129.16

CAS Registry No. 91-22-5

Synonyms: benzo[*b*]pyridine; 1-benzazine; leucoline; chinoleine.

Quinoline is a hygroscopic, colorless liquid at room temperature, with a penetrating amine-like odor (Patty's Industrial Hygiene and Toxicology, 1994). The boiling point is 237.7°C at 760 mmHg; vapor pressure is 1 mmHg at 59.7°C (Patty's Industrial Hygiene and Toxicology, 1994). Quinoline is soluble in water (60 g/L) and miscible with polar organic solvents (CHIP, 1983). Quinoline is a base that combines with strong acids to form salts, *e.g.*, quinoline hydrochloride. The hydrochloride and other strong acid salts can be expected to exist in a dissociated state in solution and *in vivo*, and thus are considered toxicologically equivalent to the free or protonated base forms. The Log octanol/water partition coefficient is 1.99 (CHIP, 1983).

2.2 Occurrence and use

Quinoline is a constituent of creosote, coal tar and certain other products derived from fossil fuels. It is also produced by combustion of a number of substances including tobacco. It is used as a solvent and a decarboxylation reagent, and as a raw material for manufacture of dyes, antiseptics, fungicides, niacin, pharmaceuticals, and 8-hydroxyquinoline sulfate (Patty's Industrial Hygiene and Toxicology, 1994). It has antimalarial activity (Merck, 1983), but does not appear to be currently used for this purpose (PDR, 1996).

The U.S. production level for quinoline reported in the U.S. Environmental Protection Agency's 1990 Toxic Substances Control Act Inventory Update was 38,000 pounds (Sherlock, 1995). In 1994, the total number of pounds released in the U.S., according to the U.S. Environmental Protection Agency's 1994 Toxics Release Inventory Public Data Release, was 91,028 pounds (US EPA, 1996).

3 DATA ON THE CARCINOGENICITY OF QUINOLINE

3.1 Studies of carcinogenicity in humans

No epidemiological studies of cancer incidence in human populations exposed to quinoline have been identified.

3.2 Studies of carcinogenicity in animals

Several bioassays of quinoline administered in feed to laboratory rats (Hirao *et al.*, 1976; Shinohara *et al.*, 1977; Hasegawa *et al.*, 1989) and a report of quinoline administered in feed to laboratory mice, hamsters and guinea pigs (Shinohara *et al.*, 1977) have been published in peer-reviewed scientific literature. Studies of quinoline administered by *s.c.* injection in rats (LaVoie *et al.*, 1988) and *i.p.* injection in mice (LaVoie *et al.*, 1987b; 1988) and studies of dermal application to mice (LaVoie *et al.*, 1984) have also been published. These carcinogenicity studies are summarized below.

3.2.1 Studies in laboratory rats

Hirao et al. (1976)

Groups of 20 male Sprague-Dawley rats were fed a standard diet supplemented with 0.05% (low dose), 0.10% (mid dose) or 0.25% (high dose) quinoline, and a control group of 6 was given the standard diet alone. All animals surviving at 40 weeks were killed and all animals were examined for tumors with the exception of those dying during the first 16 weeks. Weight gain was reduced in the mid- and high-dose groups, and survival was

poor in these groups (mean survival of 27 and 20 weeks of treatment, respectively, as compared with 40 weeks in the control group). The incidences of hemangioendotheliomas or hemangiosarcomas (combined) of the liver in treated rats are statistically significant by Fisher's exact test (Table 1), and there is a significant dose-related trend. Metastases from these tumors were found in the lungs in two animals.

TABLE 1: Incidence of hemangioendotheliomas of the liver in male Sprague-Dawley rats treated with quinoline for 40 weeks (Hirao *et al.*, 1976).

Dose (% in feed)	Incidence ¹
0	0/6
0.05	6/11 (p=0.037)
0.10	12/16 (p=0.003)
0.25	18/19 (p<0.001)

¹ p values for Fisher's exact test comparison of incidence in treatment group to that in control group are given in parentheses.

Hepatocellular carcinomas and nodular hyperplasia of the liver were also reported by the study authors. The incidence of hepatocellular carcinomas in control, low-dose, mid-dose and high-dose groups was 0/6, 3/11, 3/16 and 0/19, respectively, and the incidence of nodular hyperplasia was 0/6, 6/11, 4/16 and 0/19, respectively. The decrease in the incidence of both hepatocellular carcinomas and nodular hyperplasia at the high dose may be due to the early death of rats in this group (mean of 20 weeks following the onset of exposure).

Shinohara et al. (1977)

Groups of 25 male and 25 female Wistar rats were fed a diet containing 0.2% quinoline for 30 weeks. All animals surviving at the end of the treatment period were killed. Animals dying before 26 weeks of treatment were excluded from the experiment. The liver, spleen and kidneys of animal surviving at least 26 weeks were examined for tumors. Primary neoplasms

were reported in the liver. The incidences of hemangioendotheliomas, hepatocellular carcinomas and nodular hyperplasia were 11/15, 2/15 and 7/15, respectively, in treated males, and 7/22, 2/22 and 14/22 in treated females. There is no mention of untreated controls in this experiment; however, the presence of hemangioendotheliomas in more than 70% of males and 30% of females after 30 weeks seems biologically significant.

In a second experiment discussed in this report, 20 male Sprague-Dawley rats were fed a diet supplemented with 0.075% quinoline while a control group of 10 was fed the standard diet for 30 weeks. All rats were killed at the end of the treatment period and examined for tumors. The incidence of hemangioendotheliomas, hepatocellular carcinomas and nodular hyperplasia was 6/20, 0/20 and 9/20, respectively, in dosed rats. None of these lesions were observed in the 10 control animals. The increase in the incidence of nodular hyperplasia is statistically significant, and that of hemangioendotheliomas of borderline statistical significance (Table 2). However, the presence of these uncommon liver tumors in 30% of the rats treated for 30 weeks appears to be biologically significant.

TABLE 2: Incidence of liver tumors in male Sprague-Dawley rats treated with 0.075% quinoline in feed for 30 weeks (Shinohara *et al.*, 1977).

Tumor Type	Incidence ¹	
	0% quinoline (controls)	0.075% quinoline
hemangioendotheliomas	0/10	6/20 (p=0.065)
Hepatocellular carcinomas	0/10	0/20
Nodular hyperplasia	0/10	9/20 (p=0.012)

¹ p values for Fisher exact test relative to control group given in parentheses.

Hasegawa et al. (1989)

Groups of male Wistar rats were fed a standard diet supplemented with 0.25% quinoline for 0 (control), 4, 8, 12, 16, or 20 weeks. In the groups treated less than 20 weeks, some animals were killed at the end of the

treatment period , and some were killed at four-week intervals until all animals surviving at 20 weeks were killed. All of the animals were subjected to complete necropsy, and “main organs” were examined histopathologically for tumors. The neoplasms reported in the study were hemangioendotheliomas and hyperplastic foci of the liver. In animals killed at 20 weeks, the incidence of hemangioendotheliomas was 0/16, 0/11, 0/11, 5/12, 4/14 and 5/15 in animals dosed for 0, 4, 8, 12, 16 or 20 weeks, respectively (Table 3). The first hemangioendothelioma was seen in one of 11 animals killed at 12 weeks following 12 weeks of treatment. Hyperplastic nodules were found in 1/14 animals killed after 16 weeks of treatment and 1/15 killed after 20 weeks of treatment.

TABLE 3. Incidence of liver hemangioendotheliomas in male Sprague-Dawley rats treated with 0.25% quinoline in feed (Hasagawa *et al.*, 1989).

Weeks of treatment	Incidence in rats killed at week: ¹				
	4	8	12	16	20
0	--	--	--	--	0/12
4	0/5	0/6	0/6	0/6	0/11
8	--	0/6	0/11	0/12	0/11
12	--	--	1/11	2/12	5/12
16	--	--	--	4/14	4/18
20	--	--	--	--	5/16 (p=0.044)

¹ p values for Fisher exact test relative to control group given in parentheses.

LaVoie et al. (1988)

A group of 101 newborn male and female Sprague-Dawley rats were dosed with quinoline in dimethylsulfoxide (DMSO) by *s.c.* injection once per week for the first 8 weeks of life. The dose during week 1 and week 8 was 25.8 mg/kg, and the dose during weeks 2-7 was 12.9 mg/kg, giving a total lifetime dose of 129 mg/kg. A group of 59 newborn rats given weekly injections of

DMSO served as controls. Survival was poor in treated rats: 59% died within the first week. Animals that died before 9 months were excluded from the experiment which was terminated at 78 weeks when all surviving animals were killed and examined. No significant increases of tumor incidence at any site were found.

3.2.2 Studies in laboratory mice

Shinohara et al. (1977)

Groups of 40 male and 40 female ddY mice were fed a standard diet supplemented with 0.2% quinoline. During the first six weeks, 20 males and 20 females died from pneumonia. Animals that did not survive 26 weeks of treatment were excluded from the experiment and all animals alive at 30 weeks were killed and examined for tumors. The incidence of nodular hyperplasia, hepatocellular carcinoma and hepatic hemangioendothelioma in males was 1/10, 1/10 and 8/10, respectively, and in females were 2/10, 0/10 and 8/10. No information on a control group is presented by the authors. However, the 80% incidence of hepatic hemangioendotheliomas, which are uncommon tumors, appears to be biologically significant.

LaVoie et al. (1984)

Female SENCAR mice were given 10 dermal applications of either 0.75% quinoline in 0.1 ml acetone or 0.1 ml acetone alone. Starting 10 days after the last application, each animal was treated dermally with 2 mg of the tumor promoter, tetradecanoyl phorbol ester (TPA) twice per week for 18 weeks. The incidence of skin tumors after 18 weeks of promotion was 21/40 in treated mice and 3/39 in control mice. The increase in treated mice is highly statistically significant ($p < 0.001$ by Fisher's exact test).

LaVoie et al. (1987b)

A group of 41 male and 41 female CD-1 mice were given 0.032 mg of quinoline in DMSO on day 1 of life, 0.065 mg on day 8 and 0.129 mg on day 15 by *i.p.* injection. A control group of 35 male and 35 female rats was injected with DMSO alone on these days. Five animals of each sex in the group receiving quinoline were killed at 35 weeks, and all animals surviving

at 52 weeks were killed and examined for tumors. Animals that died during the first 35 weeks were excluded from the study. The liver, spleen and “gross lesions” from animals surviving past 35 weeks were examined histopathologically. In dosed males the incidence of hepatocellular adenomas and carcinomas in males was, respectively, 4/17 and 8/17, and in females was 1/19 and 0/10. The incidence of hepatocellular tumors in control males was 1/17 (one carcinoma) and in control females was 0/18. The increased incidence of hepatocellular tumors in treated males is statistically significant by Fisher’s exact test ($p=8.3 \times 10^{-3}$). In addition to these findings, the incidence of leukemia or lymphoma combined in female mice, 4/10, was significantly higher than the incidence, 0/18, in controls ($p=0.01$).

LaVoie et al. (1988)

A group of 56 male and female CD-1 mice were given 0.032 mg of quinoline in DMSO on day 1 of life, 0.065 mg on day 8 and 0.129 mg on day 15 by *i.p.* injection. A control group of 46 male and female rats was injected with DMSO alone on these days. All animals surviving at 22 weeks were killed and examined for tumors. Animals that died during the first six months were excluded from the study. The livers and “gross lesions” from animals surviving past six months were examined histopathologically. In dosed males the incidence of hepatocellular adenomas or carcinomas combined, 13/19 (2 carcinomas and 11 adenomas), was statistically significantly increased above the incidence 0/21 in controls. No liver tumors were seen in females. In dosed females the incidences of lung tumors, 3/27, and leukemia, 5/27, were increased above the respective incidences in controls, 0/21 and 1/21, but these increases are not statistically significant. ($p=0.17$ and $p=0.16$, respectively by Fisher’s exact test).

Weyand et al. (1993)

A group of male and female CD-1 mice were given 0.032 mg of quinoline in DMSO on day 1 of life, 0.065 mg on day 8 and 0.129 mg on day 15 by *i.p.* injection. Control groups of male and female rats was injected with DMSO alone on these days. All animals surviving at 52 weeks were killed and examined for tumors. Animals that died during the first two months were excluded from the study. The livers and lungs from animals surviving past two months were examined histopathologically. In dosed males the incidence

of hepatocellular adenomas and carcinomas was, respectively, 15/33 and 1/33. No liver tumors were found in 38 control males, in treated females or in female controls. The increased incidence of hepatocellular tumors in dosed males is highly statistically significant ($p < 0.001$ by Fisher's exact test).

3.2.3 Studies in laboratory hamsters and guinea pigs

Shinohara et al. (1977)

Groups of 25 male and 25 female Syrian golden hamsters were fed a standard diet supplemented with 0.2% quinoline. Animals that did not survive 26 weeks of treatment were excluded from the experiment, and all animals alive at 30 weeks were killed and examined for tumors. No hepatic neoplasms were found in any of the 25 males or 19 females alive at 26 weeks. The duration of this experiment is inadequate to support a conclusion that chronic administration of quinoline at this rate does not produce hepatic tumors in hamsters.

Shinohara et al. (1977)

Groups of 22 male and 22 female Hartley guinea pigs were fed a standard diet supplemented with 0.2% quinoline. Animals that did not survive 26 weeks of treatment were excluded from the experiment, and all animals alive at 30 weeks were killed and examined for tumors. No hepatic neoplasms were found in any of the 21 males or 17 females alive at 26 weeks. The duration of this experiment is inadequate to support a conclusion that chronic administration of quinoline at this rate does not produce hepatic tumors in guinea pigs.

3.3 Other relevant data

3.3.1 Genetic Toxicology

Quinoline produced mutations in the *Salmonella typhimurium* mutagenicity test in the presence but not in the absence of metabolic activation (Dong *et al.*, 1978; Eppler *et al.*, 1977; Hollstein *et al.*, 1978; Nagao *et al.*, 1979,

LaVoie *et al.*, 1991; Willes *et al.*, 1992). Quinoline also produced unscheduled DNA synthesis (UDS) in cultured rat hepatocytes (LaVoie *et al.*, 1991; Williams *et al.*, 1992). Quinoline also produced adducts with RNA and DNA when incubated in the presence of metabolic activation (Tada *et al.*, 1980). The quinoline bound to nucleic acid was released during incubation at 100 C under alkaline or acidic conditions as 3-hydroxyquinoline.

3.3.2 Structure-Activity Comparisons

When injected intraperitoneally in newborn CD-1 mice. 5-fluoroquinoline was more potent as a hepatic carcinogen than was quinoline (Weyand *et al.*, 1993). When applied to the skin of SENCAR mice as an initiator in an initiation-promotion skin tumor bioassay, 4-methylquinoline and 8-methylquinoline were approximately as potent as quinoline. However, 2-methylquinoline, 3-methylquinoline, 5-methylquinoline, 6-methylquinoline and 7-methylquinoline exhibited no significant activity (LaVoie *et al.*, 1984).

Unscheduled DNA synthesis in rat hepatocytes was produced by quinoline, 4-methylquinoline and 8-methylquinoline but was not produced by 2-methylquinoline or 5-methylquinoline. UDS was produced by 5-, 6-, 7-, and 8-fluoroquinoline but not by 2-, 3-, or 4-fluoroquinoline (LaVoie *et al.*, 1991).

Neither 5,6-dihydroxy-5,6-dihydroquinoline nor 5,6-dihydro-5,6-epoxy-quinoline induced mutations in the *Salmonella typhimurium* mutagenicity test, and they did not produce unscheduled DNA synthesis in rat hepatocytes (LaVoie *et al.*, 1987a). 2- and 3-fluoroquinoline did not produce mutations in the test, but 4-, 5-, 6-, 7- and 8-fluoroquinoline produced mutations (LaVoie *et al.*, 1991).

3.3.3 Pharmacokinetics and Metabolism

When quinoline is incubated in the presence of rat liver homogenates, the major product is 5,6-dihydroxy-5,6-dihydroquinoline. Smaller amounts of 2-hydroxyquinoline, 3-hydroxyquinoline and quinoline-N-oxide are formed (LaVoie *et al.*, 1983).

3.4 Mechanism of Carcinogenicity

The genotoxicity of quinoline demonstrated in a number of *in vitro* tests is consistent with the hypothesis that it increases the incidence of cancer by a genotoxic mechanism. Lefevre and Ashby (1992) have observed that quinoline acts as a mitogen in the liver of rats and mice but not in the liver of guinea pigs. Based on the concordance of mitogenic and carcinogenic activity in these three species, they suggested that carcinogenicity of quinoline is due to its mitogenic activity.

4 SUMMARY AND CONCLUSIONS

4.1 Summary of evidence

Administration of quinoline in feed to male rats produced a significant increase in the incidence of vascular tumors (hemangiomas or hemangiosarcomas) of the liver in two studies. Quinoline in the diet did not produce a significant increase in the incidence of tumors in hamsters or guinea pigs, but the duration of these studies was so short (30 weeks) that they are uninformative. Quinoline did not produce tumors when administered by *s.c.* injection to male and female newborn rats. When administered by *i.p.* injection to newborn mice, it produced liver tumors in males but not in females in three studies. Quinoline initiated skin tumors following dermal application to female mice.

Quinoline produced mutations in bacteria in the presence of metabolic activation, unscheduled DNA synthesis in rat hepatocytes, and DNA adducts *in vitro* in the presence of metabolic activation.

Structure-activity comparisons show several other related compounds which have been found to have tumorigenic activity that is similar to that of quinoline.

4.2 Conclusion

Based on the information reviewed in the preparation of this document, there is evidence for the carcinogenicity of *quinoline and its strong acid salts* at the

same site (liver) in two species. Observations of genetic toxicity contribute to the weight of evidence.

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